REMARKS

Claim status

Claims 1, 3, 5, 9, and 10 are amended; new claims 12-17 are added; and claim 11 is cancelled. Claims 4 and 6-8 were cancelled previously. Accordingly, claims 1-3, 5, 9, 10, and 12-17 are pending. Support for these amendments may be found in the application as-filed, *e.g.*, on page 9, lines 28-30; original claim 1; and the Examples. These amendments do not add new matter and their entry is respectfully requested.

All claim amendments are made without prejudice. Applicant reserves the right to pursue cancelled subject matter in one or more continuing applications.

Examiner interview

Applicant wishes to thank Examiners O'Dell and Desai for their availability and useful discussion in an Examiner interview on October 22, 2008. Proposed claim amendments and post-filing data were discussed. No final agreement was reached.

Enablement: claims 1-8

Of the claims cited in this rejection, only claims 1-3 and 5 are pending. Claims 1-3 and 5 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification. Specifically, the Examiner alleges that the specification, while enabling for the salts of the claimed compounds, supposedly does not enable claims to the hydrates of the salts. Applicant traverses.

Without acquiescing to the Examiner's reasoning and solely to facilitate prosecution, claims 1 and 3, from which claims 2 and 5 depend, have been amended to delete the phrase "and optionally the hydrates of the addition salts." Applicant respectfully requests that the rejection be withdrawn and the claims reconsidered.

Definiteness

Claim 11 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite. The cancellation of claim 11 renders this rejection moot.

Enablement: claims 9-11

Claims 9-11 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not enabled by the specification over their full scope. Specifically, the Examiner alleges that there are "no working examples of the treatment of a disease" in the present application, the relevant art is unpredictable, and that "[t]here is no correlation between the assays that were conducted and the many diseases described." Office Action at 6-9. The Examiner concludes that undue experimentation would be needed practice the invention in its full scope. Claim 11 is cancelled, rendering its rejection moot—however, as applied to claims 9 and 10, Applicant traverses.

The test of enablement is whether one reasonably skilled in the art could make and use the invention from Applicant's disclosure, coupled with information known in the art, without undue experimentation. *See*, e.g., *United States v. Telectronics, Inc.,* 8 U.S.P.Q.2d 1217, 1223 (Fed. Cir. 1988); M.P.E.P. § 2164.01. The Examiner bears the initial burden of factually supporting an enablement rejection, which must be based on the evidence as a whole. *See* M.P.E.P. § 2164.04. Specific technical reasons for finding a lack of enablement are always required. *Id.* Applicant respectfully avers that the Examiner has not met this initial burden and has largely provided only conclusory statements without the underlying specific technical support as to why the present claims are not enabled, as required by the M.P.E.P.

Although the Examiner presents references discussing ligand/receptor conformations, generally, (Kenakin and Onaran, *TRENDS Pharmaco. Sci.* 23:275-280 (2002)); the alleged complexity of *recombinant* 5-HT_{1A} receptor activity (Raymond, *Br. J. Pharmaco.* 127:1751-64 (1999)); and LSD's alleged affinity for 5-HT receptors (Norman *Neurochem. Intl.* 14:497-504 (1989); although this reference points out that LSD is more specific for 5-HT_2 receptors; *see* p 501, right column, first ¶), they are not applied directly to the facts of the present case. Instead, the Examiner alleges "[t]hat the factors outlined in *In re Wands* [8 USPQ2d 1400, 1404 (Fed. Cir. 1988)] mentioned above apply here..." without specifically discussing *how* they allegedly apply. Office Action at 9. The Examiner then alleges that "[i]t is vey clear that one could not make/use this very broad invention that has no working examples in this unpredictable art without undue experimentation." *Id.* The Examiner, however, has again not factually supported this assertion or adequately explained why a skilled artisan would doubt the correlation between the *in vitro* efficacy of compounds of formula 1 shown in the working examples and the disclosed methods of using them *in vivo*.

In fact, the Federal Circuit has addressed the issue of *in vitro* and *in vivo* correlations, stating that "a rigorous correlation is *not* necessary...." *Cross v. Iizuka*, 224 U.S.P.Q. 739, 747 (Fed. Cir. 1985). With regard to evidence, in general, which supports a finding of enablement, the M.P.E.P., too, instructs that the evidence "need not be *conclusive* but merely *convincing* to one skilled in the art." § 2164.05, emphasis in original.

Applicant has demonstrated the efficacy of the compounds of Formula 1 as selective agonists of 5$HT1_A$ subtype serotoninergic receptors. *See, e.g.*, page 31 of the

specification. Based on these teachings, Applicant reports that the disclosed compounds may be useful for treating, *e.g.*, depression, pain, and substance addiction, which are known to involve seratoninergic dysfunction. *See, e.g.*, pages 2-3 and 32 of the specification. Applicant also teaches pharmaceutical formulations, dosage, and modes of administration. *See, e.g.*, page 32 of the specification. Applicant respectfully submits that the application as-filed, coupled with the high level of skill in the art, more than adequately support the claimed methods of treatment. However, solely to facilitate prosecution, Applicant is providing a peer-reviewed publication and a Declaration under 37 C.F.R § 1.132 to demonstrate the *in vivo* antidepressant and analgesic activities of compounds of the invention. Applicant notes that the Federal Circuit has held that post-filing data can be submitted to prove that the disclosure was enabling when filed. *See, e.g.*, *In re Brana*, 34 U.S.P.Q.2d 1436, 1441-42 (Fed. Cir. 1995).

Maurel et al., *J. Med. Chem.* 50:5024-5033 (2007) ("Maurel" herein) teaches that, *inter alia,* (3-chloro-4-fluorophenyl)-(4-fluoro-4{[(5-methylpyrimidin-2-ylmethyl)-amino]-methyl}-piperidin-1-yl)-methanone ("F 15599" herein) dose-dependently decreased immobility time relative to vehicle in a forced swimming test, the best-established model of antidepressant-like efficacy. Maurel at 5027. During an October 22, 2008 Examiner interview, Applicant's representative inadvertently indicated that F 15599, also called compound 9 by Maurel, was the same as compound 9 of the instant application. It later came to the representative's attention that F 15599 actually corresponds to compound 5 of the instant application. *See, e.g.*, page 19 of the specification. Nevertheless, F 15599, as well as other compounds of Formula 1, clearly have potent antidepressant activity *in vivo*, as described in the as-filed application, and confirmed by Maurel with the

forced swimming test. Thus, Applicant's specification correctly ascribed antidepressant activity to the molecules of the invention.

Similarly, the attached Declaration under 37 C.F.R § 1.132 by Laurent Bardin ("the Bardin Declaration" herein) of Pierre Fabre Medicament, the assignee of the subject application, describes experiments that demonstrate F 15599's efficacy as an analgesic. Exhibit A of the Bardin Declaration is a research report on the effect of F 15599 in rats injected with formalin on their hindpaw. This formalin model of clinical inflammatory pain produces a two phase pain response, which manifests spontaneous behaviors, such as paw elevation and paw licking. *See, e.g.*, Bardin Declaration, Exhibit A at 1. F 15599 dose-dependently reduced both of these behaviors in both the early and late phase responses. Bardin Declaration, Exhibit A at 1, 5-6, and figure. Thus, F 15599 clearly has strong *in vivo* analgesic activity, as described in Applicant's disclosure, and confirmed with the formalin pain model described in the Bardin Declaration.

In view of the teachings in Applicant's application as-filed, which demonstrates the *in vitro* efficacy of the compounds of Formula 1 as selective agnosits for $5HT1_A$ subtype serotoninergic receptors, and further in view of the Maurel reference and the Bardin Declaration, which confirm that these compounds have the *in vivo* therapeutic effects described in the application as-filed, Applicant respectfully requests that the rejection be withdrawn and the claims reconsidered.

CONCLUSION

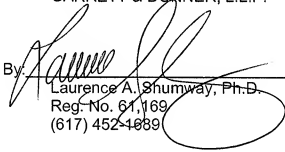
In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, L.L.P.

Dated: November 25, 2008

By: 
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Attachments:

- Maurel et al., *J. Med. Chem.* 50:5024-5033 (2007)
- Declaration under 37 C.F.R § 1.132 of Dr. Laurent Bardin, including Exhibit A thereof